

REMARKS

Claims 1-49 are pending and under consideration. With this Amendment, Claim 10 is being amended. No claims are being canceled or newly added. Thus, after entry of this Amendment, Claims 1-49 are pending and under consideration. The amendments of the claims and the various rejections raised in the Office Action are discussed in more detail, below.

The Amendments of the Claims

Claim 10 has been amended to insert a period at the end of the sentence. No new matter is added by virtue of the amendment.

Oath/Declaration

The oath/declaration is indicated as being defective because it allegedly does not identify the mailing address of each inventor.

Applicant refers the Examiner to the papers submitted on July 14, 2005 in response to the Notice of Missing Parts of Nonprovisional Application, in which Applicant submitted the executed Declaration of the inventors and an Application Data Sheet providing the mailing address of each inventor. Enclosed herewith are copies of the Transmittal, Declaration, and the Application Data Sheet as filed, and the Return Receipt Postcard stamped by the USPTO acknowledging receipt of the documents. Applicant also directs the Examiner to the USPTO PAIR information for the instant application where the Image File Wrapper is shown to contain copies of the aforementioned documents bearing the USPTO OIPE (Office of Initial Patent Examination) stamp. The provisions of 37 CFR §1.63(c) and 37 CFR §1.76, references to which are made in the Office Action, permit the use of a Declaration that does not provide the mailing addresses of the inventors if the appropriate information is provided in an Application Data Sheet in compliance with 37 CFR §1.76. In this instance, Applicant has satisfied the requirements of 37 CFR §1.63(c) and 37 CFR §1.76 by use of the Application Data Sheet, and therefore requests withdrawal of the objection.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-4, 6, 9-10, 26-28, 31-33, 36-37, 39-44, and 46-49 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”). Applicant traverses the rejection.

Anticipation of a claim is met “only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *see also* MPEP §2131 (“The identical invention must be shown in as complete detail as is contained in the . . . claim.” *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)).

Witwer describes a method of detecting target sequences utilizing a pair of oligonucleotide probes bearing fluorescent labels capable of undergoing FRET. One probe is labeled with the FRET donor, the other the FRET acceptor. The sequences of the probes are designed such that they anneal to adjacent positions of the target sequence, placing the donor and acceptor fluorophore in FRET proximity. In the assay, hybridization is detected by monitoring the fluorescence of the acceptor fluorophore following illumination of the donor molecule.

In contrast to Witwer, the instant Claim 1 recites a method of detecting a target sequence utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule. The sequences of the probes are designed such that they anneal to adjacent positions of the target sequence, placing the signal molecule and quencher molecule in quenching proximity. In the claimed method, hybridization is detected by monitoring the fluorescence of the signal molecule following illumination of the signal molecule. Thus, while Witwer basis the detection on the signal from the acceptor fluorophore, the method of Claim 1 basis its detection on the signal from the signal molecule.

As such, Witwer does not disclose each and every element of Claim 1, as required to anticipate the claim and any claims dependent therefrom. As each of the other independent

claims uses the signal probe and quencher probe combination and detects hybridization based on a signal from the signal probe, these independent claims and their corresponding dependent claims are not anticipated for at least the same reason. Accordingly, reconsideration and withdrawal of the rejection of Claims 1-4, 6, 9-10, 26-28, 31-33, 36-37, 39-44, and 46-49 under 35 U.S.C. § 102(b) is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 11-15 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”) in view of Tsourkas et al., 2002, *Nucleic Acids Res.* 30:5168 (“Tsourkas”). Applicant traverses the rejection.

In rejecting claims under 35 U.S.C. § 103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness. *See* MPEP §2142. To establish a *prima facie* case, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); *see also* MPEP §2142.

Witwer is discussed above, and will apply for all subsequent discussions pertaining to Witwer.

Tsourkas describes use of oligonucleotide probes for detecting target polynucleotides, including the use of a pair of fluorophore-labeled oligonucleotide probes that anneal to adjacent positions on a target polynucleotide. The two fluorescent labels are capable of undergoing FRET when in FRET proximity. Tsourkas detects hybridization of the probes by monitoring the fluorescence of the acceptor fluorophore upon illumination of the donor fluorophore. Thus,

detection method in Tsourkas is the same as in Witwer. Tsourkas does not teach or suggest a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Given the description in Tsourkas, the reference does not provide the necessary teaching or suggestion to correct the deficiencies in Witwer such that Witwer in view of Tsourkas fail to teach or suggest each and every element of the rejected claims. Consequently, the references are insufficient, either alone or in combination, to establish a case of *prima facie* obviousness for Claims 11-15.

Claims 11-15 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”) in view of Sokol et al., 1998, *Proc. Natl. Acad. Sci. USA* 95:11538 (“Sokol”). Applicant traverses the rejection.

Sokol describes use of oligonucleotide probes for the real time visualization of mRNA in living cells. Sokol does not teach or suggest a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on a signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, Sokol does not correct the deficiencies in the teachings of Witwer such that Witwer in view of Sokol fail to teach or suggest each and every element of the rejected claims. Consequently, Witwer in view of Sokol are insufficient, either alone or in combination, to establish a case of *prima facie* obviousness for Claims 11-15.

Claims 11, 16-22, and 38 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”) in view of Gaylord et al., 2002, *Proc. Natl. Acad. Sci. USA* 99:10954 (“Gaylord”). Applicant traverses the rejection.

Gaylord describes the use of a PNA oligonucleotide probe in combination with cationic polymers for detecting a target polynucleotide. In Gaylord, detection of the target sequence is by

FRET between a donor molecule on the cationic polymer and an acceptor fluorophore on the PNA. Since the method in Gaylord detects the signal from the acceptor fluorophore, Gaylord does not differ from Witwer with respect to the detection method. Moreover, Gaylord does not teach or suggest a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Thus, the combination of Witwer in view of Gaylord fails to teach or suggest each and every element of Claims 11, 16-22, and 38.

In fact, Gaylord specifically teaches away from use of an oligonucleotide pair that hybridizes to adjacent regions for detection of a target sequence by describing the disadvantages of using energy/electron transfer pairs for labeling two different nucleic acids (see page 10954, left column, first paragraph). Because Gaylord discourages a person of skill in the art from using a pair of adjacently hybridizing oligonucleotides for detecting a target sequence, there is no motivation to combine the references of Witwer and Gaylord. In view of the foregoing, the combination of Witwer in view of Gaylord does not support a case of *prima facie* obviousness for Claims 11, 16-22, and 38.

Claims 11, 16-20, and 38 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”) in view of Kubista et al., U.S. Patent No. 6,329,144 (“Kubista”). Applicant traverses the rejection.

Kubista describes use of labeled nucleic acid analogs, referred to as NNAs, for detecting target sequences. Kubista utilizes the enhancement of a reporter molecule signal upon interaction with a target polynucleotide to limit background signals and also detect annealing of the NNA to the target sequence. However, Kubista does not teach or suggest a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Thus, Witwer in view of Kubista fail to teach or suggest each and every element of the claimed

methods such that the references do not support a case of *prima facie* obviousness for Claims 11, 16-22, and 38.

Claims 11 and 21-23 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer et al.”) in view of Tyagi et al., U.S. Patent No. 6,277,607 (“Tyagi”). Applicant traverses the rejection.

Tyagi describes use of oligonucleotide primers that form secondary structures to reduce unwanted polymerase chain reaction amplification products. For detecting the amplified products, Tyagi uses SYBR® Green dyes in the amplification reaction. Tyagi, however, is deficient in any teaching or suggestion of a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, the descriptions in Tyagi do not correct the deficiencies in Witwer such that the combination of the references fails to teach or suggest each and every element of the rejected claims. Thus, the combination of Witwer in view of Tyagi does not support a case of *prima facie* obviousness for Claims 11 and 21-23.

Claims 24-25 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer”) in view of Singer et al., U.S. Patent No. 6,323,337 (“Singer”). Applicant traverses the rejection.

Singer describes the use of quencher labeled oligonucleotides in a polymerase chain reaction to reduce background signals from the binding of a non-specific nucleic acid stain to primer-dimers. Singer does not teach or suggest a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, the combination of Witwer in view of Singer does not teach or suggest each and every element of the instantly claimed

methods such that Witwer in view of Singer do not support a case of *prima facie* obviousness for Claims 24-25.

Claim 45 stands rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer et al.”) in view of Schalasta et al., 2000, *Infection* 28:85 (“Schalasta”). Applicant traverses the rejection.

Schalasta describes detection of amplified herpes virus DNA using SYBR® Green dye. Schalasta, however, provides no teaching or suggestion of a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, the combination of Witwer in view of Schalasta does not teach or suggest each and every element of the claims such that the references, either alone or in combination, do not establish a case of *prima facie* obviousness for Claim 45.

Claims 5 and 7-8 stands rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al., U.S. Patent No. 6,140,054 (“Witwer et al.”) in view of Caplin et al., 1999, *Biochemical* 1:5 (“Caplin”). Applicant traverses the rejection.

Caplin describes a method of designing and determining the effectiveness of oligonucleotide probes for detecting mutations. However, Caplin provides no teaching or suggestion for a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, the combination of Witwer in view of Caplin does not teach or suggest each and every element of the claimed methods such that Witwer in view of Caplin do not establish a case of *prima facie* obviousness for Claims 5 and 7-8.

Claims 29 and 34 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al. U.S. Patent No. 6,140,054 (“Witwer et al.”) in view of Marras et al., 2002, *Nucleic Acids Research* 30:e122 (“Marras”). Applicant traverses the rejection.

Marras examined the parameters for quenching of fluorescent molecules for various fluorophore-quencher combinations. Marras also describes detecting hybridization of oligonucleotides that anneal to adjacent positions of a target sequence by monitoring the fluorescence of the acceptor fluorophore of two fluorophores capable of undergoing FRET. However, Marras lacks any teaching or suggestion for a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Thus, the combination of Witwer in view of Marras does not teach or suggest each and every element of the rejected claims, and therefore does not establish a case of *prima facie* obviousness for Claims 29 and 34.

Claims 29 and 34 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al. U.S. Patent No. 6,140,054 (“Witwer”) in view of Elenitoba-Johnson et al., U.S. Patent 6,346,386 (“Elenitoba-Johnson”). Applicant traverses the rejection.

Elenitoba-Johnson describes a method of detecting the presence of a target nucleic acid by attaching a GC clamp to the target nucleic acid and determining the thermal melting transitions of the GC-clamped target nucleic acid. However, the reference fails to remedy the deficiencies in Witwer. Elenitoba-Johnson lacks any teaching or suggestion for a method utilizing a pair of nucleobase polymer probes in which one probe is labeled with a signal molecule and the other a quencher molecule, and where detection of hybridization is based on the signal from the signal probe when the two probes hybridize to adjacent positions on a target sequence. Hence, the combination of Witwer in view of Elenitoba-Johnson does not teach or suggest each and every element of the claims to support a case of *prima facie* obviousness for Claims 29 and 34.

Claims 30 and 35 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Witwer et al. U.S. Patent No. 6,140,054 (“Witwer”) in view of Witwer et al., U.S. Patent 6,245,514 (“Witwer B”). Applicant traverses the rejection.

Witwer B describes the use of a pair of oligonucleotides that hybridize to adjacent positions of a target sequence for detecting the presence of the target sequence. As with Witwer, the detection of the target sequence in Witwer B is by way of FRET between a donor fluorophore on one oligonucleotide and an acceptor fluorophore on the other oligonucleotide and monitoring of the fluorescence of the acceptor fluorophore upon illumination of the donor fluorophore. Hence, Witwer B adds nothing to the teachings of Witwer with respect to the method of detection such that the combination of Witwer in view of Witwer B fails to teach or suggest each and every element of the rejected claims. As such, Witwer in view of Witwer B do not establish a case of *prima facie* obviousness for Claims 30 and 35.

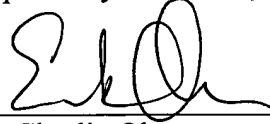
In summary, the combinations of references cited in the Office Action do not support a case of *prima facie* obviousness for any of the pending claims. Thus, Applicant requests reconsideration and withdrawal of all of the rejections under 35 U.S.C. § 103(a).

Conclusion

Claims 1-49 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees beyond those included with this response are believed to be due in connection with this Amendment. However, the Commissioner is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (Order No. 375461-036US (355414)).

Respectfully submitted,



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